

## INTRAHEPATIC OBSTRUCTIVE JAUNDICE

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OBSTRUCTIVE jaundice is amenable to surgical treatment when the obstruction is extrahepatic. In recent years it has been recognised that the obstruction may be intrahepatic and the complete picture of obstructive jaundice may be seen without obstruction of the main bile ducts. It is important to differentiate between intrahepatic and extrahepatic cholestasis in order to avoid unnecessary surgical interference. In differential diagnosis liver function tests are valuable. Liver biopsy, which can be conveniently done with a Menghini liver biopsy needle, may be diagnostic.

In view of the diagnostic difficulty a report of a case of intrahepatic cholestasis might be of interest. The significance of liver function tests and the multiple ætiology of intrahepatic cholestasis are discussed.

### CASE REPORT.

The patient was a woman aged 71 years. She was admitted to hospital on 29th March, 1962. She gave a history of painless jaundice of six weeks' duration, and she had troublesome pruritus. She had noticed the urine to be dark and the stools pale. There was no history of recent drug administration. Apart from severe icterus, clinical examination was not remarkable. The liver was not enlarged, and the gall bladder not palpable. The urine contained bile salts and bile pigment. Urobilinogen was not detected.

Liver function tests:—

#### Bilirubin

Total	-	-	-	-	25.6	mgm. %
Direct	-	-	-	-	16.9	mgm. %
Alkaline Phosphatase	-	-	-	-	4	units
Transaminase (SGOT)	-	-	-	-	20	units
Cholesterol	-	-	-	-	215	mgm. %

#### Plasma Proteins

Albumin	-	-	-	-	3.7	G. per 100 ml.
Alpha 1 Globulin	-	-	-	-	.20	G.
Alpha 2 Globulin	-	-	-	-	.50	G.
Beta Globulin	-	-	-	-	.60	G.
Gamma Globulin	-	-	-	-	.90	G.

**LIVER BIOPSY.** "It cannot be appreciated that there is any distortion of the lobular architecture. There is a very considerable inspissation of bile pigment within the intralobular bile canaliculi and this appears to be most marked in relation to the more central portions of the lobule. There is just a little variation in an occasional liver cell nucleus and in the one or two tiny portal triads is

a slight increased cellularity. Bile ducts cannot be detected. Subacute hepatitis with intralobular inspissation of bile."

Laparotomy was advised to exclude extrahepatic obstruction. There was no evidence of obstruction of the common bile duct. The liver and gall bladder appeared normal. She made a complete clinical and biochemical recovery during the two months subsequent to operation.

#### LIVER FUNCTION TESTS.

A persistent bilirubinæmia of 1.5 mg. per cent. or higher must be present before noticeable discoloration takes place. Bilirubin is a derivative of the iron-free porphyrin fraction of hæmoglobin and is formed in the reticulo-endothelial system where breakdown of erythrocytes takes place; approximately 300 mg. of bilirubin is formed daily. When liberated into the blood stream from the sites of formation, bilirubin gives an indirect van den Bergh with diazotized sulphanilic acid. It is insoluble in water and is not excreted by the kidney. Indirect-reacting bilirubin is readily taken up by hepatic cells via the sinusoids which receive blood from both the portal vein and the hepatic artery. Bilirubin is conjugated with glucuronic acid in the microsomes of the liver cells as a result of enzyme action of glucoronyl transferase. Conjugated bilirubin is water-soluble and gives a direct van den Bergh reaction.

In the intestine bilirubin undergoes reduction by bacterial action. The main product is urobilinogen which is partially re-oxidised to urobilin. Small amounts of urobilin and urobilinogen are re-absorbed from the intestine and most of this is re-excreted by the liver after re-oxidation to bilirubin. The very small amount of absorbed urobilinogen not re-excreted by the normal liver passes into the systemic blood stream and is excreted in the urine. This amount does not give the usual qualitative test for urobilinogen.

Hyperbilirubinæmia can be produced in three ways:—

- (1) By obstruction to the outflow of bile; the pigment in the plasma is chiefly conjugated bilirubin.
- (2) By excessive production of bilirubin—as in hæmolytic jaundice; the pigment in the plasma is chiefly free bilirubin. The normal liver has a great capacity to conjugate bilirubin, the amount excreted increasing in proportion to the square of the concentration in the plasma.
- (3) By inability of damaged liver cells to transmit even the normal amounts of bilirubin as in the clinical "toxic" and "infective" types of jaundice. Hepatogenous jaundice is usually associated with some degree of obstruction to the bile flow and both free and conjugated bilirubin appear in the plasma.

The van den Bergh measures the concentration of bilirubin in the plasma. Normally the concentration is between 0.1 and 0.8 mg. per 100 ml. of serum. The van den Bergh is of doubtful value in differential diagnosis of jaundice, but it is useful as a quantitative measure and is valuable in assessing progress of the case.

Bilirubinuria occurs when serum conjugated bilirubin exceeds 2 mg. per 100 ml. Urobilinogen occurs in the urine in conditions associated with excessive pro-

duction and excretion of bilirubin. One of the most difficult functions of the hepatic cells is the re-oxidation of urobilinogen to bilirubin. One of the earliest signs of hepatic cellular damage is excessive excretion of urobilinogen in the urine. Urobilinogen may be detected in the urine in cases of infective hepatitis before the development of overt jaundice.

Serum alkaline phosphatase levels usually parallel the obstructive factor of jaundice. The King and Armstrong method measures the liberation of phenol from phenyl phosphate with fifteen minutes' incubation at 37° C. and with the pH adjusted to 10.0. A plasma alkaline phosphatase greater than 35 K.A. units per 100 ml. strongly suggests obstructive jaundice; a figure below 25 units per 100 ml. suggests hepatogenous jaundice. A clear differentiation is not always possible because many cases give intermediate values.

The cholesterol of the plasma is usually increased above the normal of 240 mg. per 100 ml. in cases of obstructive jaundice.

Many tests not based directly on the production and excretion of bile constituents are of value in differential diagnosis of jaundice. In hepatogenous jaundice tests based on the metabolic functions show a greater abnormality than those based on excretory functions. In obstructive jaundice the excretory functions are more impaired.

Electrophoretic estimation of the plasma proteins is one of the most valuable of the metabolic liver function tests. The liver is an important organ in the synthesis of plasma proteins. Inflammatory and degenerative lesions of the liver are manifested by changes in the plasma proteins, viz., a decrease in the albumin and an increase in the gamma globulin. Failure of synthesis accounts for the hypoalbuminæmia. The cause of the increased gamma globulin is obscure. In obstructive jaundice there may be a rise in the beta globulin which reflects the raised plasma cholesterol.

Changes in the plasma proteins are the basis of the flocculation tests. The behaviour of a colloidal solution of several proteins towards precipitating agents depends upon the relative concentrations of the different proteins. The cephalin cholesterol and thymol turbidity reflect changes in the plasma proteins. The flocculation tests are normal in obstructive jaundice and are usually positive in hepatogenous jaundice.

Estimation of certain enzymes are of value in differential diagnosis. Serum transaminases can be assayed by their activity in transferring an amino group from glutamic acid to oxalacetic acid (SGOT) and from glutamic acid to pyruvic acid (SGPT). The transaminases are elevated in hepatogenous jaundice with parenchymal injury. Lactic dehydrogenase, which catalyses the oxidation of lactic acid to pyruvic acid, is also increased in cases of jaundice with hepatocellular damage.

Liver function tests must be interpreted in relationship to the clinical findings. An accurate diagnosis can be established in approximately 90 per cent. of cases. Liver biopsy may be diagnostic in doubtful cases. It is important that the clinician should appreciate the difficulty which confronts the pathologist in his interpre-

tation of the hepatic changes in sections of liver biopsy. The main difficulty arises in the distinction between intrahepatic and extrahepatic cholestasis. In extrahepatic cholestasis there may be multiplication of bile ductules in the portal zones which show a predominantly polymorph infiltration reflecting the cholangitis. In intrahepatic cholestasis there is inspissation of bile pigment within the intralobular bile canaliculi and the bile ductules are flattened and inconspicuous. In intrahepatic cholestasis due to drugs the portal zones may show an eosinophilic infiltration.

A block of the bile duct may be shown by the technique of percutaneous transhepatic cholangiography. In patients with extrahepatic cholestasis a bile duct may be punctured. The procedure carries a risk of biliary peritonitis and is not recommended.

#### INTRAHEPATIC CHOLESTASIS.

The mechanism of jaundice in intrahepatic cholestasis is doubtful. Electron microscopy has shown distortion of the microvilli lining the bile canaliculi. An additional factor may be a disturbance of intracellular bilirubin transport from the hepatic cell into the bile canaliculus. As a consequence, bile accumulates in the intralobular bile canaliculi. Obstruction of the bile ductules by infiltrates in the portal zones is unlikely to be a factor.

One important cause of intrahepatic cholestasis is the hepatotoxicity of drugs. Certain drugs, including chloroform, carbon tetrachloride, tetrachlorethylene, ethyl chloride, benzene derivatives, certain metallic poisons, iproniazid and other hydrazine monoamine-oxidase inhibitors, isonicotinic acid, and pyrazinamide are direct hepato-cellular poisons which produce centrilobular liver necrosis. This state is reflected by high serum transaminase levels and abnormal plasma protein pattern. Hepatic damage is often associated with acute renal tubular necrosis.

In contrast to this severe hepatocellular jaundice due to drugs is the more benign intrahepatic drug cholestasis which is manifested by painless, afebrile, obstructive jaundice. The liver is not enlarged and not tender. Liver biopsy may be equivocal and such cases may come to laparotomy which reveals the main bile ducts to be patent.

There are two types of cholestatic drug jaundice. The first type is caused by a hypersensitivity reaction and may follow administration of chlorpromazine ("largactil") and other phenothiazine derivatives such as promazine ("sparine") and trifluoperazine ("stelazine"), para-aminosalicylic acid, thiouracil, chlorpropamide ("diabinese"), and nitrofurantoin ("furadantin"). Cholestatic jaundice develops in about 1 per cent. of patients taking chlorpromazine. Jaundice may follow a single dose or one day's treatment. The initial manifestations may be leucopenia, eosinophilia, drug fever, and drug rash. Recovery usually takes place within one to four weeks after the drug has been discontinued. Occasionally jaundice is much more prolonged and the clinical picture in such cases simulates primary biliary cirrhosis. The serum cholesterol and alkaline phosphatase levels are high from the outset.

The second type of acute intrahepatic drug cholestasis may complicate treatment with methyltestosterone and other related steroids, including nore-

thandrolone ("nilevar") and methandienone ("dianabol"). This type is not due to hypersensitivity but is a straightforward consequence of dosage and duration of administration. The clinical picture of steroidal jaundice resembles that seen in chlorpromazine jaundice. Liver biopsy reveals inspissation of bile in the canaliculi but there is no portal-zone cellular reaction as occurs with chlorpromazine jaundice.

Another cause of intrahepatic obstructive jaundice is virus hepatitis. Jaundice persists for several months and recovery is complete. This is in contrast to subacute hepatitis and cirrhosis which may complicate an attack of virus hepatitis and is conditioned by methionine deficiency. The atypical hepatitis with intrahepatic cholestasis is the variety which has been called cholangiolitic hepatitis. According to Dubin the ætiological agent is a variant of the virus of infective hepatitis. In cholangiolitic hepatitis there is no biochemical evidence of hepatocellular damage. The serum transaminase and the plasma protein pattern are normal; the serum alkaline phosphatase is usually slightly raised. The patient, in whom intrahepatic cholestasis is due to cholangiolitic hepatitis, sometimes shows a dramatic response to corticosteroid therapy. Prednisolone, 40 mg. daily for four days, may cause a fall in the serum bilirubin level. The action of corticosteroid in alleviating the jaundice is obscure.

A rare type of intrahepatic cholestasis occurs during pregnancy.

Primary biliary cirrhosis is another type of intrahepatic cholestasis of obscure mechanism. The onset is insidious and liver biopsy shows marked infiltration in the portal zones.

#### SUMMARY.

The difficulty in diagnosis of intrahepatic obstructive jaundice may lead to unnecessary surgical intervention because an incorrect diagnosis of extrahepatic obstruction is made.

It is essential to elicit any history of recent drug administration.

Fever, rigors, and leucocytosis indicate extrahepatic obstruction and reflect secondary infection in the dilated ducts.

Liver biopsy may be diagnostic but it is sometimes difficult to distinguish between intrahepatic and extrahepatic cholestasis.

Response to a trial of corticosteroid therapy would indicate intrahepatic obstruction.

In doubtful cases serial liver function tests should be performed at weekly intervals during a period of three to four weeks' observation.

Some patients may require laparotomy to establish a definitive diagnosis.

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